Respiratory Medicine (2007) **101**, 875–881

ELSEVIER

respiratoryMEDICINE

HISTORICAL REVIEW

100 years of respiratory medicine: Pneumonia

Francesco Blasi*, **Stefano Aliberti**, **Maria Pappalettera**, **Paolo Tarsia**

Istituto di Tisiologia e Malattie dell'Apparato Respiratorio, University of Milan, Ospedale Maggiore Fondazione IRCCS Policlinico, Mangiagalli e Regina Elena, Via F. Sforza 35, Milan 20122, Italy

KEYWORDS
Pneumonia;
Historical review;
Diagnosis;
Therapy

Summary
In this review, we aim to lead the readers through the historical highlights of pathophysiological concepts and treatment of pneumonia. Understanding the aetiology, the risk factors and the pathophysiology influenced our management approaches to pneumonia. Pneumonia is still associated with significant morbidity and mortality, presents in a variety of healthcare settings and imposes a considerable cost to healthcare services. Guidelines have been issued by international and national scientific societies in order to spread the scientific knowledge on this important disease and to improve its management.

Introduction

Pneumonia has been recognized as a disease entity since remote times, with definitions of the condition traceable in ancient Greek, Roman, and Arabic writings. Definitive recognition of the etiologic role of microorganisms in pneumonia, and the identification of *Streptococcus pneumoniae* as the most common causative agent was only achieved roughly 120 years ago. The introduction of antibiotics has obviously modified the impact of the disease on society, but pneumonia is still associated with considerable morbidity and mortality. Over the last decade, important step forwards have been made in improving pneumonia management through the availability of scores for patient admission decisions, timing and choice of empirical antibiotic treatment, and vaccination prevention strategies. The development of international and local guidelines has helped condense the ever-expanding scientific knowledge on pneumonia into statements and recommendations of clinical use for the bedside physician. This is certainly welcome as studies indicate that patient management is amenable to improvement in aspects such as hospitalization of mild pneumonia cases with low mortality risk, lack of association between microbiological investigation and pneumonia severity, inadequate antimicrobial treatment with over-treatment of non-severe cases, and under-treatment of severe cases.[1]

Epidemiology and clinical presentation

Community-acquired pneumonia (CAP) is a common health problem that may still be life threatening in an age of wide availability of effective antibiotic therapy. The annual incidence rate rises from 6/1000 in the 18–39 age group to 34/1000 in people aged 75 years and over.[2] Geographical variations in incidence rates are present, with, for example, lower rates being recorded in Southern Europe compared to Northern countries.[3] Hospital admission is deemed

*Corresponding author. Tel.: +39 02 50320621; fax: +39 02 50320628.
E-mail address: francesco.blasi@unimi.it (F. Blasi).

0954-6111/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.rmed.2007.02.016

necessary in 20–40% of cases, with 5–10% of these patients being admitted to an intensive care unit (ICU). Overall mortality from CAP is 5–10%.[4]

In addition to increasing age, comorbidities have long been recognized as risk factors for CAP.[5] Currently identified risk factors for CAP include male sex, chronic obstructive pulmonary disease (COPD), cigarette smoking, heart disease, occupational dust exposure, and single marital status.[6]

Up until the early 1940s textbooks of medicine recognized that pneumonia could present only as lobar pneumonia or bronchopneumonia, with the small residuum dubbed as ''unresolved''. Pneumonia has largely changed its character from the old classical lobar pneumonia to ''atypical'' clinical and radiological descriptions.[7] In a case series in the 1950s, Wingfield[8] found ''atypical'' lobar or lobular consolidation in over 50% of patients, with classical lobar pneumonia in less than 10% of cases.

As from the 1980s, the classification of pneumonia based on lists of different pathogens was abandoned in favour of a more practical classification that helps to guide investigation, management and therapy: CAP,[9] hospital-acquired (or nosocomial) pneumonia,[10] and pneumonia in the immunocompromised host.[11]

Common clinical symptoms of CAP include cough, fever, chills, fatigue, dyspnea, rigors, and pleuritic chest pain. Cough may be persistent and dry, or it may produce sputum in no more than 50% of patients. Other presentations may include headache and myalgia. Physical examination may reveal dullness to percussion of the chest, crackles or rales on auscultation, bronchial breath sounds.

Etiology

Most studies investigating the microbiological causes of patients with CAP involved cases admitted to hospital, with only a limited number of studies have investigated etiology of CAP in the community. However, available information regarding mild CAP suggests that overall microbial etiology is not substantially different from that of hospitalized patients, with few important exceptions.[12]

Analysis of CAP etiologic studies reveals variations in terms of the frequency of individual microorganism, probably related to differences in studied populations (associated with age or other risk factors), geographical area, and the presence of intercurrent epidemics. Results may also be biased by the use/non-use of specific samples and microbiological methods, or primary attention devoted to particular agents (e.g. viruses or intracellular bacteria).

Regardless of the extent of microbiological investigation, diagnostic yield in CAP rarely reaches 60% of cases. Therefore, in all studies, the most frequent category includes cases with no pathogen identified. This finding is probably attributable to multiple factors including presence of organisms undetectable by conventional microbiological methods, ambulatory antibiotic pretreatment, presence of as yet unknown microorganisms, and non-infective diseases that mimic pneumonia. Age $\geqslant$70 years, and presence of cardiac or renal comorbidity have been identified as factors associated with undetermined etiology.[13] Interestingly, the introduction of sensitive new diagnostic techniques does not appear to associate with a meaningful increase in diagnostic yield compared to the etiologic determination rates of 40 years ago.[14]

Etiology of out-patient pneumonia

It has been estimated that 50–80% of pneumonia cases may be treated outside the hospital and this group therefore constitutes the majority of patients with CAP. The most important pathogens causing pneumonia in this setting are *Streptococcus pneumoniae*, intracellular bacilli such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*, followed by *Haemophilus influenzae*.[15–20] *Streptococcus pneumoniae* is more common among older patients or those with underlying disease whereas *M. pneumoniae* is more often detected in patients younger than 50 years and without important comorbid conditions.[21] Viruses are reported to be involved in 5–20% of cases, either as sole pathogens or as part of a mixed infection. Influenza viruses are the agents most commonly associated with pneumonia.[22] Unlike adults, approximately 60% of lower respiratory tract infections maybe viral in origin in children. Incidence varies in different age groups, reaching as much as 80% during the first years of life and up to school age, and thereafter decreasing to 40–50%. In many cases viral infections are complicated by superimposed bacterial involvement. Metapneumovirus is a recently described paramyxovirus, which appears to be a potentially important viral respiratory tract pathogen, causing pneumonia in both adults and children.[23]

M. pneumoniae may present cyclic epidemics every 4–7 years during which a peak incidence of 30% may be reached, with more sporadic cases being registered at other times.[24] This agent is also particularly common in younger individuals, and may be among the most common bacteria in adolescent/young adult populations. *Staphylococcus aureus*, *Legionella* and gram-negative enteric bacteria are uncommon in disease managed outside the hospital.

Etiology of hospital-treated pneumonia

Between 20% and 50% of patients with pneumonia are hospitalized for treatment.[18] *Streptococcus pneumoniae* is the most commonly identified pathogen in cases of CAP, incidence ranging from 3% to 76%.[25–27] Moreover, since even a single dose of antibiotic treatment prior to pneumonia diagnosis may hinder pneumococcal detection, it is felt that this organism is probably the leading cause of pneumonia of unknown etiology.[28] Bacteremia may develop in 10–20% of cases, and this pathogen alone accounts for about two thirds of all cases of bacteremic pneumonia cases, with mortality rates approaching 30%,[29] and rarely evolving into necrotizing pneumonia.[30]

H. influenzae and *M. pneumoniae* are frequently the second most common pathogens, and some but not all studies attribute a greater propensity for the former agent among smokers and COPD patients. *C. pneumoniae* accounts for 3–20% of CAP cases depending on several factors such as setting of the studied population, age group examined, and diagnostic methods used.[31,32] The clinical course may vary from a mild, self-limiting illness to a severe form of pneumonia, particularly in elderly patients, and in patients with coexisting cardiopulmonary diseases. This agent is

present as part of a coinfection involving other bacterial agents in approximately 30% of cases.[28]

Among the most relevant differences between etiology of community- and hospital-treated pneumonia is the substantially higher incidence of *L. pneumophila* cases among the latter. The incidence of *Legionella* infection in different studies ranges from 0.5% to 6% of CAP cases in most hospital-based series.[33]

Etiology of severe pneumonia

A limited number of episodes of CAP (roughly 2% of all cases) are sufficiently severe to require admission to an ICU. Along with *Streptococcus pneumoniae*, *Legionella* spp. are identified consistently as among the most common causative agents of severe CAP, particularly among patients sufficiently severe to require intubation.[34–37] *Legionella* was 1 of 2 major respiratory tract pathogens in patients with CAP who required admission to the ICU, according to 7 of 9 recent reviews.[38] In terms of frequency, *Streptococcus pneumoniae* and *L. pneumophila* are followed at a distance by *Staphylococcus aureus* and gram-negative enteric bacteria, particularly *Pseudomonas aeruginosa*.[39] Aspiration pneumonia is a common cause of severe pneumonia, particularly among alcoholics, injections drug abusers, persons with poor dental hygiene and the elderly. Etiology is generally polymicrobial with both Gram-positive and Gram-negative anaerobes playing a leading role in this form of pneumonia.[40] Viral infections are uncommon, and are mostly due to influenza virus with bacterial *Streptococcus pneumoniae* or *Staphylococcus aureus* superinfection.

Etiology of nursing home-acquired pneumonia

Elderly residents of long-term care facilities have been found to have a particular spectrum of pathogens. In a study of 104 patients age 75 years and older with severe pneumonia, El-Solh found *Staphylococcus aureus* (29%), enteric gram-negative rods (15%), *Streptococcus pneumoniae* (9%), and *Pseudomonas* species (4%) as the most frequent causes of nursing home-acquired pneumonia.[37] In another study of 52 long-term care residents aged 70 years and above who failed to respond to first line antibiotics, MRSA (33%), gram-negative enterics (24%), and *Pseudomonas* species (14%) were the most frequent pathogens isolated by invasive diagnostics (bronchoscopy).[41] In the latter study, 72% had at least two comorbidities whereas 23% had three or more.

Mixed infections

Mixed community-acquired lower respiratory tract infections are more common than previously recognized.[42,43] In the setting of pneumonia, polymicrobial infections are present at all ages, although there may be important differences. In children mixed viral–bacterial are highly prevalent, with an increase in bacterial-atypical bacterial co-infections after school-age that appears to persist into adult-hood. Elderly patients, on the one hand are at risk for Gram-negative and anaerobic polymicrobial aspiration pneumonia, and on the other are more prone to bacterial superinfections following influenza infection. Presentation characteristics do not help to distinguish between monomicrobial and polymicrobial infections, although the latter tend to be associated with greater underlying diseases and may be linked to a more severe clinical course.

Streptococcus pneumoniae is the leading pathogen in the etiology of CAP. It is important to bear in mind that between 16% and 45% of pneumococcal infections are mixed, generally involving an atypical bacteria or a virus. The potential importance of mixed infections is highlighted by recent retrospective studies showing that combined antimicrobial therapy that includes a macrolide, given empirically, may reduce mortality associated with bacteremic pneumococcal pneumonia.[44] Recent treatment recommendations have incorporated the idea that atypical pathogen infection should be considered in all patient groups, sometimes in the form of mixed infection.

The observed rate of mixed viral–bacterial infections in pneumonia may also lead to treatment considerations. In individual patients during influenza epidemics, use of rapid detection techniques such as real-time PCR may allow the use of effective neuraminidase inhibitors such as oseltamivir and zanamivir with 36–48 h of symptom onset, thus reducing the emergence of secondary bacterial complications (including pneumonia) by up to 50%.[45] On a larger scale, the known association between influenza and excess mortality for pneumonia underscores the importance of widespread influenza vaccination in eligible patients as this has shown to reduce pneumonia hospitalizations and deaths.[46]

Diagnostic methods

The traditional microbiological approach to CAP relies on staining or culture of easily obtainable samples such as respiratory secretions, blood or pleural fluid. Up to about 30 years ago, additional culture methods such as mouse intraperitoneal homogenized sputum inoculation were still in use.[14] Serological determinations are the basic method to identify atypical bacterial and viral pathogens difficult to grow in culture. The results of applying the above techniques is far from optimal, with etiologic diagnosis being reached in a minority of cases.[13] The results of diagnostic procedures such as microbiological cultures or serological tests have delays of days to weeks and are therefore not suitable guides to therapy in an early stage of the disease. Concerns regarding low yield, expenses, and delay in response have raised questions on the cost-effectiveness of systematic use of microbiological testing in patients with pneumonia. Furthermore, studies disagree about the impact of laboratory based microbiological testing on the outcome of CAP.[47,48] Introduction of novel techniques such as urinary antigen detection and nucleic acid amplification tests allows rapid identification of a number of causative agents, but further effort is needed to identify rapid (almost instantaneous), easily performed, accurate, cost-effective diagnostic tests.

There is considerable debate as to the extent of microbiological work up that should be undertaken in patients presenting with CAP. Arguments against microbiological studies include the low yield in many reports, and the evidence that, even in patients with severe CAP, outcome is not improved by establishing a specific etiologic diagnosis.[49] On the other hand there is a perception that the quality of microbial studies in the context of pulmonary infections has

declined substantially in the current era compared to 3 decades ago, and this poses questions on whether this change is acceptable or reversible.[50] There are a number of potential advantages in endeavoring to identify causative agents, for individual patients, society, and in economic terms.[51] Nonetheless, performing diagnostic tests should not result in the delay of initiation of appropriate therapy as an increased 30-day CAP mortality was registered when administration of the first dose of antibiotic was delayed more than 8 h from the time of arrival in hospital, and antibiotic treatment prior to 4 h following admission reduces length of hospital stay.[52,53]

Recent guidelines have provided a series of recommendations that constitute a reasonable framework for microbiological investigations in CAP patients.[54–57] All guidelines recognize that the extent of microbiological work up should vary according to the site of management of CAP, with cases managed in the community requiring minimal assessment compared to hospitalized patients, and subjects with severe pneumonia admitted to the ICU deserving maximal efforts to achieve etiological diagnosis. The Infectious Diseases Society of America (IDSA) guidelines[54] place a greater emphasis on the identification of the responsible agent to guide antibiotic therapy as compared with other international guidelines.[55,56]

In general terms, outpatients with CAP should have a chest radiograph (whenever possible), but sputum culture and Gram stain are generally not required outside epidemiological surveys. Sputum examination may be considered in patients who do present purulent sputum, particularly if they do not respond to empirical antibiotic treatment.

All hospitalized patients with CAP should undergo chest radiography, routine blood chemistry and blood counts, and blood gas analysis. All guidelines recommend two sets of blood cultures. Blood cultures have a low sensitivity and a high specificity, and are positive in about 4–18% of untreated CAP patients, most commonly associated with severe illness.[58] The yield is generally greater if the blood specimen is collected prior to the patient having received antibiotic treatment.[59] Assessment of specific factors associated with greater likelihood of positive blood culture may reduce the overall burden of tests performed with little negative impact on the diagnostic yield.[60] Gram stain and culture are advised if the patient is able to expectorate purulent samples and has not received prior antibiotic therapy.[61,62] This is particularly true if a drug-resistant pathogen, or an organism not covered by usual empiric antibiotic treatment, is suspected. Although sputum testing cannot be used to focus initial empiric antibiotic therapy, it may be used to redirect treatment once results have been obtained. The pneumococcal urinary antigen assay is considered an acceptable test to augment standard diagnostic methods for *Streptococcus pneumoniae* detection.[63] Similarly, testing for *Legionella* is considered appropriate in hospitalized patients with enigmatic pneumonia, or unresponsive to β-lactam treatment.[64] A very recent study found that addition of rapid urine antigen tests for *Streptococcus pneumoniae* and *L. pneumophila* increased the diagnostic yield by 17.8%.[65] Thoracentesis should be performed in the presence of significant pleural effusion, with stain, culture, pH, and leukocyte count.[66] There is some debate as to how extensively serology should be applied to hospitalized patients. Serologic determinations for *C. pneumoniae*, *M. pneumoniae*, and *L. pneumophila* may be considered in patients unresponsive to β-lactam treatment, during outbreaks, or when there is strong suspicion of an ''atypical'' pathogen on clinical radiographic, or epidemiological grounds.

In severe CAP cases, subjects requiring admittance to an ICU, or those failing initial empiric antibiotic all the following are recommended: blood culture, respiratory sample Gram stain and culture, thoracenthesis. On the basis of local availability pneumococcal and *Legionella* urinary determinations should be performed together with serological testing for atypical pathogens and viruses. In this setting addition of invasive techniques such as bronchoscopy (protected brush specimen and bronchoalveolar lavage)[67,68] or transthoracic needle aspiration,[69] depending on local expertise, may be of use.

Hospital admission

The decision whether outpatient or inpatient management is needed for a patient with CAP is of primary importance. Hospital admission requirements depend on many possible variables including disease severity, coexisting illness, risk factors, adequate family support/home facilities, and patient compliance to treatment. Recently, two main tools have been put forward to objectively assess pneumonia severity and guide admission decisions.

The pneumonia severity index (PSI) was developed in the United States and validated on over 38,000 patients.[70] The system was primarily developed to detect patients with low mortality risk who could de safely treated as outpatients. Patients with CAP are stratified into one of five categories with a score system based on age, presence of coexisting illnesses, and vital signs. Patients in classes I–III present a low mortality risk ($<3\%$), whereas classes IV–V have a high mortality risk (8–30%). These finding have been extrapolated to guide hospital admission decisions, with inpatient treatment suggested for higher mortality PSI classes. Application of this score system has been shown to reduce avoidable hospital admission without increasing mortality.[71] A number of limitations have been recognized. Age affects overall score very heavily, potentially underestimating need for hospitalization in younger patients. The score may also overestimate the need for hospitalization and use of expensive resources by a heavy emphasis on age and coexisting illnesses rather than on severity features of pneumonia. A total of 20 variables are involved in generating the score, making the system rather cumbersome and unfit for rapid mnemonic recall at the patient bedside.

The British Thoracic Society guidelines advocate the use of a clinical score that identifies of a limited number of variables (three clinical, one laboratory) recognized as strong adverse prognostic factors for pneumonia. The factors include age over 65, mental confusion, elevated urea nitrogen, and respiratory rate >30 breaths per minute, condensed in the acronym CURB-65. Patients who do not present any of the factors have been shown to have a mortality risk close to 1%, and may be considered for outpatient management, whereas presence of two or more adverse factors suggest the need for hospital admission.[72,73]

The CURB-65 scoring system is undoubtedly simpler than the PSI and measures pneumonia disease severity more directly. However, some adjustment must be made for the presence of comorbidities, not directly accounted for by the score. It has been suggested that both systems should be used conjunctly. Either can successfully define low risk patients not requiring hospitalization. In addition to the PSI, vital sign and CURB-65 severity evaluation should be added. When employing the CURB-65, an assessment of comorbid illness and its stability should be added.[74]

Antibiotic treatment

Recent international guidelines have provided a framework for initial empirical antibiotic selection in patients with CAP.

For outpatients with pneumonia, North American guidelines suggest the use of a macrolides, doxycycline, or a fluoroquinolone agent, as appropriate empiric outpatient treatment for low-risk patients (i.e., otherwise young healthy individuals). Alternatives to these agents in low-risk patients are amoxicillin/clavulanate and some second-generation cephalosporins (e.g., cefuroxime, cefpodoxime, or cefprozil).[54,56] Recent European guidelines on lower respiratory tract infection suggest tetracycline and amoxicillin are antibiotics of first choice.In case of hypersensitivity a newer macrolide like azithromycin, roxithromycin or clarithromycin is a good alternative in countries with low pneumococcal macrolide resistance.When there are clinically relevant bacterial resistance rates against all first choice agents, treatment with levofloxacin or moxifloxacin may be considered.[57] Oral treatment is generally suggested.

When treating CAP patients who require hospitalization, consensus between guidelines from both sides of the Atlantic is more consistent. Generally an association between a beta-lactam (amoxicillin, amoxicillin/clavulanate, non-antipseudomonal II or III generation cephalosporin) plus a macrolide are suggested, with a respiratory fluoroquinolone (levofloxacin, moxifloxacin) as alternative monotherapy. In patients with risk factors for *P. aeruginosa* pnemonia, combination therapy is generally advocated, involving an antipseudomonal cephalosporin or acylureidopenicillin/β-lactamase inhibitor or carbapenem, together with ciprofloxacin.

Future strategies

Current treatment of pneumonia is largely based on timely prescription of adequate antibiotic therapy. However, antimicrobial treatments are hampered by the ever-increasing problem of resistant strains, and the prospects for future antibiotics preparations are gradually slimming. Alternative strategies are therefore needed based on a better knowledge of microbial pathogenetic mechanisms and a more complete comprehension of host defense systems.

The complexity of the mechanisms and mediators involved in inflammation and infection is increasingly being unraveled, and the genetic regions controlling these factors have been partly elucidated. Soluble and membrane-based receptors have been identified that are capable of recognizing non-mammalian microbial motifs and mobilizing close to instantaneous inflammatory reactions towards infection. An increasing number of peptides exerting antimicrobial activity are being recognized in airway secretions, associated with chemokines, cytokines, proteinase inhibitors, and surfactant proteins.

Genetic polymorphisms in genes for important inflammatory molecules such as tumor necrosis factor, the interleukin-1 family, interleukin-10, and angiotensin converting enzyme, as well as molecules involved in innate immunity antigen recognition, such as the mannose-binding lectin, CD-14, and Toll-like receptors (TLRs), have been investigated as potential modifiers in the natural history of sepsis and pneumonia.[75] Better knowledge of underlying genetic traits may help identify patients at greater risk of severe complications following infection. On the other hand, overactivation of innate immune responses may be associated with excessive inflammation and tissue damage such as may be observed in sepsis.

In the future it may be possible to modulate the innate immune response in order to downplay pathways leading to tissue inflammation while enhancing mechanisms involved in microbial elimination. Antimicrobial peptides (AMPs) present in airway surface fluid are effector molecules of the innate immunity with direct antimicrobial and mediator function. They provide an initial host defense mechanism that protects mucosal and dry epithelial surfaces of all multicellular organisms. Several diseases in humans and laboratory animals are characterized by impairment in the function of an AMP.[76] AMPs qualify as prototypes of innovative drugs that might be used as antibiotics, antipolysaccharide drugs or modifiers of inflammation. Antibiotics based on these naturally occurring mammalian peptides might elicit fewer allergic reactions compared to conventional antibiotics. Synthetic analogs of AMPs may evolve into novel and independent classes of antibiotics.[77]

Recently identified mammalian TLRs are capable of distinguishing pathogen from self-components, triggering cytokine production, and expressing co-stimulatory molecules necessary for lymphocyte activation. Central to the signaling cascade triggered by TLRs is the activation of transcription factors such as nuclear factor κB (NF-κB) and activator protein-1 (AP-1), key regulators of inflammatory and immune responses.[78] Given their central role in activating and modulating host responses to infection, and acting as a bridge between innate and adaptive immunity, TLRs are being currently studied as potential therapeutic targets. Soluble forms of TLRs may be made to bind and neutralize natural ligands before they activate potent proinflammatory responses in the host. Alternatively, antibodies or molecules similar to natural ligands could be employed in order to bind with TLR extracellular or intracellular domains, though failing to activate intracellular signaling. This may result in inhibition of proinflammatory cascades initiated by TLRs, while retaining TLR-related protective responses.[79]

Hepatocyte growth factor (HGF) is a is a heterodimeric protein produced, among others, by lung fibroblasts and macrophages, that promotes proliferation of type II epithelial cells following lung injury, restoring alveolar and bronchial epithelial integrity.[80] Recently, HGF levels have been tested in serum and exhaled breath condensate of patients with pneumonia and other non-respiratory conditions.[81] During the first days of the infections, pneumonia

patients had higher HGF serum levels compared to controls, followed by a marked drop at days 4–7 that persisted up to 4–6 weeks. Conversely, exhaled breath HGF levels, were also higher than controls during the acute phase, but showed non-drop through all the observation period, suggesting that local production of this factor is active during pneumonia. Future studies will be needed to determine whether local inhalation of HGF may be considered ad an adjuvant treatment, particularly in severe or complicated pneumonia cases.

References

1. Ewig S, Seifert K, Kleinfeld T, et al. Management of patients with community-acquired pneumonia in a primary care hospital: a critical evaluation. *Respir Med* 2002;**94**:556–63.
2. Woodhead MA, Macfarlane JT, McCracken JS, Rose DH, Finch RG. Prospective study of the aetiology and outcome of pneumonia in the community. *Lancet* 1987;**1**:671–4.
3. Viegi G, Pistelli R, Cazzola M, et al. Epidemiological survey on incidence and treatment of community acquired pneumonia in Italy. *Respir Med* 2006;**100**:46–55.
4. Hoare Z, Lim WS. Pneumonia: update on diagnosis and management. *Br Med J* 2006;**332**:1077–9.
5. Oswald NC, Simon G, Shooter RA. Pneumonia in hospital practice. *Br J Dis Chest* 1961;**55**:109–18.
6. Farr BM, Bartlett CL, Wadsworth J, Miller DL. Risk factors for community-acquired pneumonia diagnosed upon hospital admission. *Respir Med* 2000;**94**:954–63.
7. Taylor AB. The management of respiratory infection. *Br J Dis Chest* 1960;**54**:157–9.
8. Wingfield AL. The changing pattern of pneumonia. *Br J Tuberc Dis Chest* 1951;**45**:27–31.
9. MacFarlane J. Community-acquired pneumonia. *Br J Dis Chest* 1987;**81**:116–27.
10. White R, Dilworth P. Pneumonia in hospital. *Br J Dis Chest* 1988;**82**:121–6.
11. Pozniak AL, Swinburn CR, Johnson N. Management of AIDS pneumonia. *Br J Dis Chest* 1985;**79**:105–14.
12. Michetti G, Pugliese C, Bamberga M, Ori BM, et al. Community-acquired pneumonia: is there a difference in etiology between hospitalized and out-patients? *Minerva Med* 1995;**86**:341–51.
13. Ewig S, Torres A, Ángeles Marcos M, Angrill J, et al. Factors associated with unknown aetiology in patients with community-acquired pneumonia. *Eur Respir J* 2002;**20**:1254–62.
14. Bath JC, Boussard GP, Calder MA, Moffat AJ. Pneumonia in hospital practice in Edinburgh 1960–1962. *Br J Dis Chest* 1964;**58**:1–16.
15. Macfarlane J, Holmes W, Gard P, Macfarlane R, et al. Prospective study of the incidence, aetiology and outcome of adult lower respiratory tract illness in the community. *Thorax* 2000;**56**:109–14.
16. Almirall J, Bolibar I, Vidal J, Sauca G, et al. Epidemiology of community-acquired pneumonia in adults: a population-based study. *Eur Respir J* 2000;**15**:757–63.
17. Bochud PY, Moser F, Enrad P, et al. Community-acquired pneumonia. A prospective outpatient study. *Medicine* 2001;**80**:75–87.
18. Jokinen C, Heiskanen L, Juvonen H, Kallinen S, et al. Microbial etiology of community-acquired pneumonia in the adult population of 4 municipalities in eastern Finland. *Clin Infect Dis* 2001;**32**:1141–54.
19. Lagerström F, Bader M, Foldevi M, Fredlund H, et al. Microbiological etiology in clinically diagnosed community-acquired pneumonia in primary care in Örebro, Sweden. *Clin Microbiol Infect* 2003;**9**:645–52.
20. Marrie TJ, Poulin-Costello M, Beecroft MD, Herman-Gnjidic Z. Etiology of community-acquired pneumonia treated in an ambulatory setting. *Respir Med* 2005;**99**:60–5.
21. File Jr TM. Community-acquired pneumonia. *Lancet* 2003;**362**: 1991–2001.
22. de Roux A, Marcos MA, Garcia E, Mensa J, et al. Viral community-acquired pneumonia in nonimmunocompromised adults. *Chest* 2004;**125**:1343–51.
23. Falsey AR, Erdman D, Anderson LJ, Walsh EE. Human metapneumovirus infections in young and elderly adults. *J Infect Dis* 2003;**187**:785–90.
24. Marrie TJ, Peeling RW, Fine MJ, Singer DE, et al. Ambulatory patients with community-acquired pneumonia: the frequency of atypical agents and clinical course. *Am J Med* 1996;**101**: 508–15.
25. Jones RN, Croco MA, Kugler KC, Pfaller MA, Beach ML. Respiratory tract pathogens isolated from patients hospitalized with suspected pneumonia: frequency of occurrence and antimicrobial susceptibility patterns from the SENTRY Antimicrobial Surveillance Program (United States and Canada, 1997). *Diagn Microbiol Infect Dis* 2000;**37**:115–25.
26. Logroscino CD, Penza O, Locicero S, Losito G, et al. Community-acquired pneumonia in adults: a multicentric observational AIPO study. *Monaldi Arch Chest Dis* 1999;**54**:11–7.
27. Sopena N, Sabria M, Pedro-Botet ML, Manterola JM, Socan M, Marinic-Fiser N, et al. Microbial aetiology of community-acquired pneumonia in hospitalised patients. *Eur J Clin Microbiol Infect Dis* 1999;**18**:777–82.
28. Ruiz-Gonzalez A, Falguera M, Nogues A, Rubio-Caballero M. Is *Streptococcus pneumoniae* the leading cause of pneumonia of unknown etiology? A microbiologic study of lung aspirates in consecutive patients with community-acquired pneumonia. *Am J Med* 1999;**106**:385–90.
29. Banks RA, George RC, McNicol MW. Pneumococcal pneumonia with bacteraemia. *Br J Dis Chest* 1984;**78**:352–7.
30. Isaacs RD. Necrotizing pneumonia in bacteraemic pneumococcal infection. *Br J Dis Chest* 1986;**80**:295–6.
31. Blasi F, Cosentini R, Raccanelli R, Rinaldi A, et al. Emerging pathogens of community-acquired pneumonia: a two-year prospective study. *J Chemother* 1995;**7**(Suppl. 4): 115–6.
32. Schneeberger PM, Dorigo-Zestma JW, van der Zee A, van Bon M, van Opstal JL. Diagnosis of atypical pathogens in patients hospitalized with community-acquired respiratory infection. *Scan J Infect Dis* 2004;**36**(4):269–73.
33. Stout JE, Yu VL. Legionellosis. *N Engl J Med* 1997;**337**:682–7.
34. Feldman C, Ross S, Goolam Mohamed A, et al. The aetiology of severe community-acquired pneumonia and its impact on initial, empiric, antimicrobial chemotherapy. *Respir Med* 1995;**89**:187–92.
35. Rello J, Bodi M, Mariscal D, Navarro M, et al. Microbiological testing and outcome of patients with severe community-acquired pneumonia. *Chest* 2003;**123**:174–80.
36. Gowardman J, Trent L. Severe community acquired pneumonia: a one-year analysis in a tertiary referral intensive care unit. *N Z Med J* 2000;**113**:161–4.
37. El Solh AA, Sikka P, Ramadan F, Davies J. Etiology of severe pneumonia in the very elderly. *Am J Respir Crit Care Med* 2001;**163**:645–51.
38. Vergis EN, Yu VL. New directions for future studies of community-acquired pneumonia: optimizing impact on patient care. *Eur J Clin Microbiol Infect Dis* 1999;**18**:847–51.
39. Garau J, Gomez L. Pseudomonas aeruginosa pneumonia. *Curr Opin Infect Dis* 2003;**16**(2):135–43.
40. Leroy O, Vandenbussche C, Coffinier C, Bosquet C, et al. Community-acquired aspiration pneumonia in intensive care units. Epidemiological and prognosis data. *Am J Respir Crit Care Med* 1997;**156**:1922–9.

41. El Solh AA, Aquilina AT, Dhillon RS, Ramadan F, Nowak P, Davies J. Impact of invasive strategy on management of antimicrobial treatment failure in institutionalized older people with severe pneumonia. *Am J Respir Crit Care Med* 2002;**166**:1038–43.
42. de Roux A, Ewig S, Garcia E. Mixed community-acquired pneumonia in hospitalised patients. *Eur Respir J* 2006;**27**: 795–800.
43. Gutiérrez F, Masiá M, Rodriguez JC. Community-acquired pneumonia of mixed etiology: prevalence, clinical characteristics, and outcome. *Eur J Clin Microbiol Infect Dis* 2005;**24**: 377–83.
44. Waterer GW. Monotherapy versus combination antimicrobial therapy for pneumococcal pneumonia. *Curr Opin Infect Dis* 2005;**18**:157–63.
45. Treanor JJ, Hayden FG, Vrooman PS, et al. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. US Oral Neuraminidase Study Group. *JAMA* 2000;**283**:1016–24.
46. Nordin J, Mullooly J, Poblete S, et al. Influenza vaccine effectiveness in preventing hospitalizations and deaths in persons aged 65 years or older in Minnesota, New York, and Oregon: data from 3 health plans. *J Infect Dis* 2001;**184**:665–70.
47. Theerthakarai R, El-Halees W, Ismail M, Solis RA, Khan MA. Non value of the initial microbiological studies in the management of non severe community-acquired pneumonia. *Chest* 2001; **119**:181–4.
48. Wunderink RG, Waterer GW. Appropriate microbiological testing in community-acquired pneumonia. *Chest* 2001;**119**:5–7.
49. Leroy O, Santre C, Beuscart C, Georges H, et al. A five-year study of severe community-acquired pneumonia with emphasis on prognosis in patients admitted to an ICU. *Intensive Care Med* 1995;**21**:24–31.
50. Bartlett JC. Decline in microbial studies for patients with pulmonary infections. *Clin Infect Dis* 2004;**39**:170–2.
51. Bartlett JG, Dowell SF, Mandell LA, File TM, et al. Practice guidelines for the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2000;**31**:347–82.
52. Meehan TP, Fine MJ, Krumholz HM, et al. Quality of care, process, and outcomes in elderly patients with pneumonia. *JAMA* 1997;**278**:2080–4.
53. Houck PM, Bratzler DW, Nsa W, et al. Timing of antibiotic administration and outcomes for medicare patients hospitalized with community-acquired pneumonia. *Arch Intern Med* 2004;**164**:637–44.
54. Mandell LA, Bartlett JG, Dowell SF, File TM, Musher DM. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. *Clin Infect Dis* 2003;**37**:1405–33.
55. British Thoracic Society. Guidelines for the management of community-acquired pneumonia in adults. *Thorax* 2001; **56**(Suppl 4):1–64.
56. Niederman MS, Mandell LA, Anzueto A, et al. Guidelines for the management of adults with community-acquired pneumomia (American Thoracic Society). *Am J Respir Crit Care Med* 2001; **163**:1730–54.
57. Woodhead M, Blasi F, Ewig S, et al. Guidelines for the management of lower respiratory tract infections. *Eur Respir J* 2005;**26**:1138–80.
58. Skerrett SJ. Diagnostic testing for community-acquired pneumonia. *Clin Chest Med* 1999;**20**:531–48.
59. Glerant JC, Hellmuth D, Scmit JL, Ducroix JP, Jounieaux V. Utility of blood cultures in community-acquired pneumonia requiring hospitilization: influence of antibiotic treatment before admission. *Respir Med* 1999;**93**:208–12.
60. Metersky ML, Ma A, Bratzler DW, Houck PM. Predicting bacteremia in patients with community-acquired pneumonia. *Am J Respir Crit Care Med* 2004;**169**:342–7.
61. Roson B, Carratala J, Verdaguer R, Dorca J, Manresa F, Gudiol F. Prospective study of the usefulness of sputum Gram stain in the initial approach to community acquired pneumonia requiring hospitalization. *Clin Infect Dis* 2000;**31**:869–74.
62. Musher DM, Montoya R, Wanahita A. Diagnostic value of microscopic examination of Gram-stained sputum and sputum cultures in patients with bacteremic pneumococcal pneumonia. *Clin Infect Dis* 2004;**39**:165–9.
63. Gutierrez F, Rodriguez JC, Ayelo A, et al. Evaluation of the immunochromatographic Binax NOW assay for detection of *Streptococcus pneumoniae* urinary antigen in a prospective study of community-acquired pneumonia in Spain. *Clin Infect Dis* 2003;**36**:286–92.
64. Murdoch DR. Diagnosis of Legionella infection. *Clin Infect Dis* 2003;**36**:64–9.
65. Andreo F, Dominguez J, Ruiz J, et al. Impact of urine antigen tests to determine the etiology of community-acquired pneumonia in adults. *Respir Med* 2006;**100**:884–91.
66. Smith PR. What diagnostic tests are needed for community acquired pneumonia. *Med Clin North Am* 2001:1381–95.
67. Marquette CH, Wallet F, Nevière R, et al. Usefulness of direct examination of protected brush specimen in the diagnosis of pneumonia in ventilated patients. *Eur Respir J* 1994;**7**:105–13.
68. Rasmussen TR, Korsgaard J, Moller JK, Sommer T, Kilian M. Quantitative culture of bronchoalveolar lavage fluid in community-acquired lower respiratory tract infections. *Respir Med* 2001;**95**:885–90.
69. Ishida T, Hashimoto T, Arita M, Osawa M, Tachibana H, Nishioka M, et al. Efficacy of transthoracic needle aspiration in community-acquired pneumonia. *Intern Med* 2001;**40**:873–7.
70. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 1997;**336**:243–50.
71. Marrie TJ, Lau CY, Wheeler SL, et al. A controlled trial of a critical pathway for treatment of community-acquired pneumonia. CAPITAL Study Investigators. Community-acquired pneumonia intervention trial assessing levofloxacin. *JAMA* 2000;**283**:749–55.
72. Lim WS, Lewis S, Macfarlane JT. Severity prediction rules in community-acquired pneumonia: a validation study. *Thorax* 2000;**55**:219–23.
73. Capelastegui A, Espana PP, Quintana JM, et al. Validation of a predictive rule for the management of community-acquired pneumonia. *Eur Respir J* 2006;**27**:151–7.
74. Niederman MS, et al. *Eur Respir J* 2006;**27**:9–11.
75. Wunderink RG, Waterer GW. Genetics of sepsis and pneumonia. *Curr Opin Crit Care* 2003;**9**:384–9.
76. Zasloff M. Antimicrobial peptides of multicellular organisms. *Nature* 2002;**415**:389–95.
77. Brown KL, Hancock RE. Cationic host defense (antimicrobial) peptides. *Curr Opin Immunol* 2006;**18**:24–30.
78. O'Neill LA. How Toll-like receptors signal: what we know and what we don't know. *Curr Opin Immunol* 2006;**18**:3–9.
79. Yeh WC, Chen NJ. Another Toll road. *Nature* 2003;**424**:736–7.
80. Panos RJ, Rubin JS, Csaky KG, et al. Keratinocyte-growth factor and hepatocyte growth factor/scatter factor and heparin-binding growth factor for alveolar type II cells in fibroblast-conditioned medium. *J Clin Invest* 1993;**92**:969–77.
81. Nayeri F, Millinger E, Nilsson I, et al. Exhaled breath condensate and serum levels of hepatocyte growth factor in pneumonia. *Respir Med* 2002;**96**:115–9.